Chapter 8

Haemophilus influenzae type b

HAEMOPHILUS INFLUENZAE WAS FIRST DESCRIBED BY PFEIFFER in 1892. During a major outbreak of influenza, he found the bacteria in the sputum of patients, and proposed a causal association between this species and the clinical syndrome known as influenza. The organism was given the name *Haemophilus* by Winslow, et al., in 1920. It was not until 1933 that Smith, et al., established that influenza was caused by a virus and that *H. influenzae* was a cause of secondary infection.

In the 1930s, Margaret Pittman showed that *H. influenzae* could be isolated in encapsulated and unencapsulated forms. She identified six capsular types (a-f), and observed that virtually all isolates from cerebrospinal fluid (CSF) and blood were of the capsular type b.

Before the introduction of effective vaccines, *H. influenzae* type b (Hib) was the leading cause of bacterial meningitis and other invasive bacterial disease among children <5 years of age. Almost all serious Hib infections were among children <5 years of age; approximately one in 200 children developed invasive Hib disease before the age of 5 years. Two-thirds of cases were among children <18 months of age.

***Haemophilus influenzae* type b**

- **Severe bacterial infection, primarily in infants**
- **During late 19th century believed to cause influenza**
- **Immunology and microbiology clarified in 1930s**

Haemophilus influenzae

Haemophilus influenzae is a gram-negative coccobacillus. It is generally aerobic, but can grow as a facultative anaerobe. In vitro growth requires accessory growth factors. These include "X" factor (hemin) and "V" factor (nicotinamide adenine dinucleotide [NAD]).

Chocolate agar media are used for isolation. *H. influenzae* will generally not grow on blood agar, which lacks NAD.

Haemophilus influenzae

- **Aerobic gram-negative bacteria**
- **Polysaccharide capsule**
- **Six different serotypes (a-f) of polysaccharide capsule**
- **95% of invasive disease caused by type b**

***Haemophilus influenzae* type b Pathogenesis**

- **Organism colonizes nasopharynx**
- **In some persons organism invades bloodstream and cause infection at distant site**
- **Antecedent URI may be a contributing factor**

The outermost structure of *H. influenzae* is composed of polyribosyl-ribitol phosphate (PRP), a polysaccharide, which is responsible for virulence and immunity. Six antigenically and biochemically distinct capsular polysaccharide serotypes have been described, which are designated types a through f. Type b organisms account for 95% of all strains that cause invasive disease.

Pathogenesis

The organism enters the body through the nasopharynx. Organisms colonize the nasopharynx and may remain only transiently or for several months in the absence of symptoms ("asymptomatic carrier"). Hib strains occur in the nasopharynx with a prevalence of 0.5%-3% in normal infants and children, uncommonly in adults. Nontypable (unencapsulated) strains are also frequent inhabitants of the human respiratory tract and are generally non-invasive.

In some persons the organism causes an invasive infection. The exact mode of invasion to the blood stream is unknown. Antecedent viral or mycoplasma infection of the upper respiratory tract may be a contributing factor. The bacteria spread in the bloodstream to distant sites in the body. Meninges are especially likely to be affected.

The most striking feature of Hib disease is **age-dependent susceptibility**. Passive protection of some infants is provided by transplacentally acquired maternal IgG antibodies and breast-feeding during the first 6 months of life. Peak attack rates occur at 6-7 months of age, declining thereafter. Hib disease is uncommon beyond 5 years of age. The presumed reason for this age distribution is the acquisition of humoral immunity to Hib with increasing age.

Antibodies to Hib capsular polysaccharide are protective. The precise level of antibody required for protection against invasive disease is not clearly established. However, a geometric mean titer (GMT) of 1 µg/mL 3 weeks postvaccination correlated with protection in studies following vaccination with unconjugated PRP vaccine and suggested long-term protection from invasive disease.

Acquisition of both anticapsular and serum bactericidal antibody is inversely related to the age-specific incidence of Hib disease.

In the pre-vaccine era, most children acquired "natural" immunity by 5-6 years of age through asymptomatic infection by Hib bacteria. Since only a relatively small proportion of children carry Hib at any time, it has been postulated that exposure to organisms that share common antigenic structures with the capsule of Hib (so-called "cross-reacting organisms") may also stimulate the development of anticapsular antibodies against Hib. Natural exposure to Hib also induces antibodies to outer membrane proteins, lipopolysaccharides, and other antigens on the surface of the bacterium.

The genetic constitution of the host may also be important in susceptibility to infection with Hib. Risk for Hib disease has been associated with a number of genetic markers, but the mechanism of these associations is unknown. No single genetic relationship regulating susceptibility or immune responses to polysaccharide antigens has yet been convincingly demonstrated.

Clinical Features

Invasive disease caused by *H. influenzae* type b can affect many organ systems. The most common types of invasive disease are meningitis, epiglottitis, pneumonia, arthritis, and cellulitis.

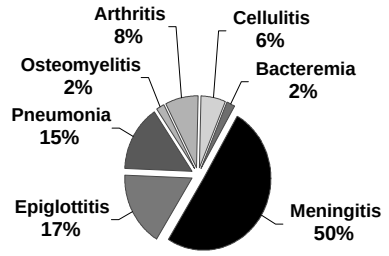
Meningitis is infection of the membranes covering the brain and is the most common clinical manifestation of invasive Hib disease, accounting for 50%-65% of cases. Hallmarks of Hib meningitis are fever, decreased mental status, and stiff neck. The mortality rate is 2%-5%, despite appropriate antimicrobial therapy. Neurologic sequelae occur in 15%-30% of survivors.

Epiglottitis is an infection and swelling of the epiglottis, the tissue in the throat that covers and protects the larynx during swallowing. Epiglottitis may cause life-threatening airway obstruction.

Septic arthritis (joint infection), **cellulitis** (rapidly progressing skin infection which usually involves face, head, or neck), and **pneumonia** (which can be mild focal or severe empyema) are common manifestations of invasive disease.

Osteomyelitis (bone infection), and **pericarditis** (infection of the sac covering the heart) are less common forms of invasive disease.

***Haemophilus influenzae* type b**
Clinical manifestations



***Haemophilus influenzae* type b**
Meningitis

- **Accounted for approximately 50% - 65% of cases**
- **Hearing impairment or neurologic sequelae in 15%-30%**
- **Case-fatality rate 2%-5% in spite of effective antimicrobial therapy**

Otitis media and acute bronchitis due to *H. influenzae* are generally caused by nontypable strains. Hib strains account for only 5%-10% of *H. influenzae* causing otitis media.

The case-fatality rate for invasive *H. influenzae* disease is 2% to 5%.

Laboratory Diagnosis

A **gram stain** of an infected body fluid may demonstrate small gram-negative coccobacilli suggestive of invasive Haemophilus disease. Cerebrospinal fluid (CSF), blood, pleural fluid, joint fluid, and middle ear aspirates should be cultured on the appropriate media. A positive **culture** for *Haemophilus influenzae* establishes the diagnosis.

All isolates of *Haemophilus influenzae* should be serotyped. This is an extremely important laboratory procedure that should be performed on every isolate of *Haemophilus influenzae*, especially those obtained from children <15 years of age. This test determines whether an isolate is type b, and is important because only type b is potentially vaccine preventable. Serotyping is usually done by either the state health department laboratory or a reference laboratory.

Antigen detection may be used as an adjunct to culture, particularly in the diagnosis of patients who have been partially treated with antimicrobials and the organism may not be viable on culture. Two types are available. **Latex agglutination** is a rapid, sensitive, and specific method to detect Hib capsular polysaccharide antigen in CSF, serum, urine, pleural fluid, joint fluid, etc. **Counterimmunoelectrophoresis (CIE)** is similar to latex agglutination, but is less sensitive, takes longer, and is more difficult to perform.

Medical Management

***Haemophilus influenzae* type b**
Medical Management

- **Immediate treatment with chloramphenicol or an effective 3rd generation cephalosporin**
- **Ampicillin-resistant strains now common throughout the United States**
- **Hospitalization required**

Hospitalization is generally required. Antimicrobial therapy with chloramphenicol or an effective third-generation cephalosporin (cefotaxime or ceftriaxone) should be begun immediately. Treatment course is usually 10 to 14 days.

Ampicillin-resistant strains of Hib are now common throughout the United States. Children with life-threatening illness in which Hib may be the etiologic agent should not receive ampicillin as initial empiric therapy.

Epidemiology

Occurrence

Hib disease occurs worldwide. However, the incidence outside the United States and Europe has not been determined.

***Haemophilus influenzae* type b Epidemiology**

• Reservoir	Human Asymptomatic carriers
• Transmission	Respiratory droplets
• Temporal pattern	Bimodal- peaks Sept-Dec and March-May
• Communicability	Generally limited but higher in some circumstances

Reservoir

Humans are the only known reservoir. Hib does not survive in the environment on inanimate surfaces.

Transmission

Primary mode is presumably by respiratory droplet spread, although firm evidence for this mechanism is lacking.

Temporal pattern

Several studies have described a bimodal seasonal pattern in the United States, with one peak between September and December, and a second peak between March and May. The reason for this bimodal pattern is not known.

Communicability

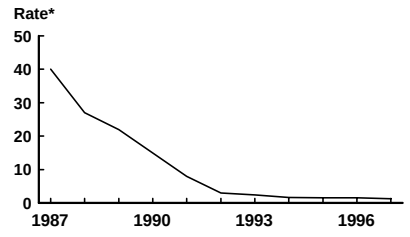
The contagious potential of invasive Hib disease is considered to be limited. However, certain circumstances, particularly close contact with a case (*e.g.*, household, day-care, or institutional setting) can lead to outbreaks or direct secondary transmission of the disease.

Secular Trends in the United States

Haemophilus influenzae infections became nationally reportable in 1991. Serotype-specific reporting continues to be incomplete. However, most reported infections probably represent type b disease.

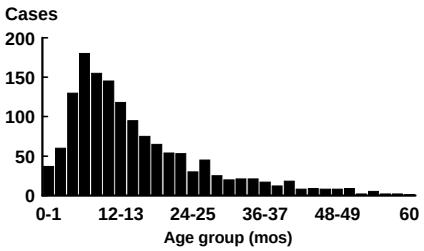
Prior to the availability of national reporting data, several areas carried out active surveillance for *H. influenzae* disease, which allowed estimates of disease nationwide. In the early 1980s, it was estimated that about 20,000 cases occurred annually in the United States, primarily among children younger than 5 years of age (40-50 cases per 100,000 population). The incidence of invasive Hib disease began to fall dramatically in the late 1980s, coincident with licensure of conjugate Hib vaccines, and has declined by >99% compared to the prevaccine era. Only 144 confirmed cases of Hib invasive disease were reported in the two years period 1996-1997.

Indicence* of Invasive Hib Disease Among Children <5 Years of Age, 1987-1997



*rate per 100,000 children <5 years of age, estimated

***Hemophilus influenzae* type b, 1986**
Incidence by age group



***Haemophilus influenzae* type b disease in the 1990s**

- **144 confirmed Hib cases reported in 1996-1997**
- **Incidence has fallen 99% since prevaccine era**
- **Most recent cases in unvaccinated or incompletely vaccinated children**

***Hemophilus influenzae* type b**
Risk factors for invasive disease

- **Exposure factors**
  - **household crowding**
  - **large household size**
  - **day care attendance**
  - **low socioeconomic status**
  - **low parental education**
  - **school-aged siblings**
- **Host factors**
  - **race/ethnicity**
  - **chronic disease**

There also is good evidence that Hib vaccines decrease the rate of carriage of Hib among vaccinated children, therefore decreasing the chance that unvaccinated children will be exposed.

Incidence is strikingly age-dependent. Up to 60% of invasive disease occurs before age 12 months, with a peak occurrence in children 6-11 months of age. Children over 60 months of age account for <10% of invasive disease.

In 1996-1997, approximately 48% of children less than 5 years of age with confirmed invasive Hib disease were less than 6 months of age, and too young to have completed a three-dose primary vaccination series. Fifty-two percent were age 6 months or older, and were eligible to have completed the primary vaccination series. Of these age-eligible children, 64% were either incompletely vaccinated or their vaccination status was unknown.

In 1996-1997, 5 (4%) of 115 children with known outcome died. All children who died were less than 6 months of age, and had received one or no Hib vaccine doses.

Risk factors for Hib disease include host factors and exposure factors that increase the likelihood of exposure to Hib. Exposure factors include household crowding, large household size, day-care attendance, low socioeconomic status, low parental education levels, and school-aged siblings. Host factors include race/ethnicity (elevated risk in blacks, Hispanics, Native Americans — possibly confounded by socioeconomic variables that are associated with both race/ethnicity and Hib disease), chronic diseases (*e.g.*, sickle cell anemia, antibody deficiency syndromes, malignancies, especially during chemotherapy), and possibly gender (male > female).

Protective factors (effect limited to <6 months of age) include breast-feeding and passively acquired maternal antibody.

Secondary Hib disease is defined as illness within 1-60 days following contact with an ill child, and accounts for less than 5% of all invasive Hib disease. Among **household contacts**, six studies have found a secondary attack rate of 0.3% in the month following disease onset of the index case, which is about 600-fold higher than the risk for the general population. Attack rates varied substantially with age, from 3.7% among children under 2 years of age to 0% among contacts over the age of 6 years. In these household contacts, 64% of secondary cases occurred within the first week (excluding the first 24 hours) of disease onset in the index case, 20% during the second week, and 16% during the third and fourth weeks.

There are conflicting data regarding the risk of secondary transmission among **day-care contacts**. Secondary attack rates have varied from 0% to as high as 2.7%. Most studies seem to suggest that day-care contacts are at relatively low risk for secondary transmission of Hib disease.

Haemophilus influenzae type b Vaccine

Characteristics

A pure polysaccharide vaccine (HbPV) was licensed in the United States in 1985. The vaccine was not effective among children younger than 18 months of age. Estimates of efficacy in older children varied widely, from 88% to -69% (a negative efficacy implies greater disease risk for vaccinees than nonvaccinees). HbPV was used until 1988, but is no longer available in the United States.

***Haemophilus influenzae* type b Polysaccharide Vaccine**

- **Available 1985-1988**
- **Not effective in children <18 months of age**
- **Effectiveness in older children variable**

The characteristics of the Hib polysaccharide were similar to other polysaccharide vaccines (*e.g.*, pneumococcal, meningococcal). The response to the vaccine was typical of a T-independent antigen, most notably an age-dependent response, and poor immunogenicity in children <2 years of age. In addition, no boost in antibody titer was observed with repeated doses, the antibody which was produced was relatively low-affinity IgM, and switching to IgG production was poor.

Polysaccharide Vaccines

- **Age-related immune response**
- **Not consistently immunogenic in children 2 years old**
- **No booster response**
- **Antibody with less functional activity**

Haemophilus influenzae type b *polysaccharide-protein conjugate vaccines*

Conjugation is the process of chemically bonding a polysaccharide (a poor antigen) to a protein "carrier," which is a more effective antigen. This process changes the polysaccharide from a T-independent to a T-dependent antigen, and greatly improves immunogenicity, particularly in young children. In addition, repeat doses of Hib conjugate vaccines elicit booster responses, and allow maturation of class-specific immunity with predominance of IgG antibody. The Hib conjugates also cause carrier priming and elicit antibody to "useful" carrier protein.

Polysaccharide Conjugate Vaccines

- **Stimulates T-dependent immunity**
- **Enhanced antibody production, especially in young children**
- **Repeat doses elicit booster response**
- **Antibody is biologically active in vitro**

The first Hib conjugate vaccine (PRP-D, ProHIBIT) was licensed in December 1987. This vaccine was not consistently immunogenic in children <18 months of age, and is not recommended for use in infants.

Hib Conjugate Vaccines

- **Pure polysaccharide vaccines (1985-1989) not effective in infants**
- **3 products licensed for use in infants**
- **Chemically and immunologically different**

Since 1990, four additional conjugate Hib vaccines have been licensed for use in infants as young as 6 weeks of age. Three of these vaccines are chemically and immunologically distinct (ActHIB and OmniHIB are identical vaccines marketed by different companies). Several combination vaccines that contain Hib conjugate vaccine are also available (see below).

***Haemophilus influenzae* type b Conjugate Vaccines**

Vaccine	Protein Carrier	Manufacturer
PRO-D* (ProHIBIT™)	Diphtheria toxoid	Connaught Labs
HbOC* (HibTITER™)	Mutant diphtheria protein	Lederle/Praxis
PRP-T* (ActHIB™ or Omni HIB™)	Tetanus toxoid	Pasteur Mérieux Vaccins
PRP-OMP* (PedvaxHIB®)	Meningococcal group B outer membrane protein	Merck & Co., Inc.

Immunogenicity and vaccine efficacy

All three Hib conjugate vaccines licensed for use in infants are highly immunogenic. More than 95% of infants will develop protective antibody levels after a primary series of 2 or 3 doses. Clinical efficacy has been estimated at 95% to 100%. Invasive Hib disease in a completely vaccinated infant is very rare.

Hib vaccine is immunogenic in patients with increased risk for invasive disease, such as those with sickle-cell disease, leukemia, human immunodeficiency virus (HIV) infection, and in those who have had splenectomies. However, in persons with HIV infection, immunogenicity varies with stage of infection and degree of immunocompromise. Efficacy studies have not been performed in populations with increased risk of invasive disease.

Vaccination Schedule and Use

All infants, including those born prematurely, should receive a primary series of conjugate Hib vaccine (separate or in combination), beginning at 2 months of age. The number of doses in the primary series depends on the type of vaccine used. A primary series of PRP-OMP (PedvaxHIB) vaccine is two doses; HbOC (HibTiTER) and PRP-T (ActHIB) require a three-dose primary series (See table below). A booster is recommended at 12-15 months regardless of which vaccine is used for the primary series.

ACIP-Recommended *Haemophilus influenzae* type b (Hib) Routine Vaccination Schedule

Vaccine	2 months	4 months	6 months	12-15 months
HbOC	Dose 1	Dose 2	Dose 3	Booster
PRP-T	Dose 1	Dose 2	Dose 3	Booster
PRP-OMP	Dose 1	Dose 2		Booster

The optimal interval between doses is 2 months, with a **minimum interval** of 4 weeks. At least 8 weeks should separate the booster dose from the previous (2nd or 3rd) dose. Hib vaccines may be given simultaneously with all other vaccines.

Recent data suggest that if Hib conjugate vaccines are given before 6 weeks of age, they may induce immunologic tolerance to additional doses of Hib vaccine. A dose given before 6 weeks of age may make the child incapable of responding to subsequent doses. As a result, **Hib vaccines, including combination vaccines that contain Hib conjugate, should never be given to a child younger than 6 weeks of age.**

***Haemophilus influenzae* type b Vaccine**

- **Vaccination at <6 weeks of age may induce immunologic tolerance to Hib antigen**
- **Minimum age 6 weeks**
- **Minimum interval 4 weeks**

All 3 conjugate Hib vaccines licensed for use in infants are interchangeable. A series that includes vaccine of more than one type will induce a protective antibody level. If it is necessary to change vaccine type, three doses of any combination constitute the primary series. Any licensed conjugate vaccine may be used for the booster dose regardless of what was received in the primary series.

***Haemophilus influenzae* type b Vaccine Interchangeability**

- **All conjugate Hib vaccines interchangeable for primary series and booster dose**
- **3 dose primary series if more than one brand of vaccine used**

Unvaccinated children 7 months of age and older may not require a full series of 3 or 4 doses. The number of doses a child needs to complete the series depends on the child's current age, and does not depend on the number of prior doses of Hib vaccine the child has received.

Detailed Vaccination Schedule for *(Haemophilus influenzae)* type b Conjugate Vaccines

Vaccine	Age at 1st dose (months)	Primary Series	Booster
HbOC/PRP-T	2-6	3 doses, 2 months apart	12-15 months
	7-11	2 doses, 2 months apart	12-18 months
	12-14	1 dose	2 months later
	15-59	1 dose	- -
PRP-OMP	2-6	2 doses, 2 months apart	12-15 months
	7-11	2 doses, 2 months apart	12-18 months
	12-14	1 dose	2 months later
	15-59	1 dose	- -
PRP-D (Connaught)	15-59	1 dose	- -

***Haemophilus influenzae* type b Vaccine Delayed Vaccination Schedule**

- **Children starting late may not need entire 3 or 4 dose series**
- **Number of doses child requires depends on current age**
- **All children 15-59 months of age need at least 1 dose**

HbOC or PRP-T

Previously unvaccinated infants aged 2-6 months should receive three doses of vaccine administered 2 months apart, followed by a booster dose at age 12-15 months, at least 2 months after the last vaccination. Unvaccinated children aged 7-11 months should receive two doses of vaccine, 2 months apart, followed by a booster dose at age 12-18 months, at least 2 months after the last vaccination. Unvaccinated children aged 12-14 months should receive two doses of vaccine, at least 2 months apart. Any previously unvaccinated child aged 15-59 months should receive a single dose of vaccine.

PRP-OMP

Unvaccinated children aged 2-11 months should receive two doses of vaccine, 2 months apart, followed by a booster dose at 12-18 months of age, at least 2 months after the last dose. Unvaccinated children aged 12-14 months should receive two doses of vaccine, 2 months apart. Any previously unvaccinated child 15-59 months of age should receive a single dose of vaccine.

PRP-D

One dose of PRP-D may be administered to unvaccinated children aged 15-59 months. This vaccine may be used as a booster dose at 12-18 months of age following a two- or three-dose primary series, regardless of the vaccine used in the primary series. This vaccine is not licensed for use among infants because of its limited immunogenicity and variable protective efficacy in this age group.

Children with a **lapsed Hib immunization** series (that is, children who have received one or more doses of Hib-containing vaccine but are not up-to-date for their age) may not need all the remaining doses of a 3 or 4 dose series.

The ACIP does not address the issue of vaccination of children with a lapsed Hib series. However, the 1997 edition of the American Academy of Pediatrics Red Book does provide some guidance. Information from the Red Book is summarized in the following table.

Hib Vaccination Schedule for Children with Lapsed Series (from 1997 AAP Red Book)

Current Age (mos)	Prior Vaccination History	Recommended Regimen
7-11	1 dose	1 dose at 7-11 mos, booster at least 2 mos later at 12-15 mos
7-11	2 doses of HbOC or PRP-T	Same as above
12-14	2 doses before 12 mos	1 dose of any licensed conjugate
12-14	1 dose before 12 mos	2 doses of any licensed conjugate separated by 2 mos
15-59	Any incomplete schedule	1 dose of any licensed conjugate

Hib invasive disease does not always result in development of protective anti-PRP antibody levels. **Children <24 months of age who develop invasive Hib disease** should be considered unimmunized and receive Hib vaccine as recommended in the schedule. Vaccination of these children should start as soon as possible during the convalescent phase of the illness. The schedule should be completed as needed for the child's age.

***Haemophilus influenzae* type b Vaccine**
Vaccination following invasive disease

- **Children <24 months may not develop protective antibody after invasive disease**
- **Vaccinate during convalescence**
- **Complete series for age**

Vaccination of older children and adults

In general, **children >59 months of age** do not need Hib vaccination. The majority of these children are immune to Hib, probably from asymptomatic infection as infants. However, some older children and adults are at increased risk for invasive Hib disease and may be vaccinated. These high risk persons include those with functional or anatomic asplenia (e.g., sickle cell disease, postsplenectomy), immunodeficiency (in particular, persons with IgG2 subclass deficiency), immunosuppression from cancer chemotherapy, and infection with human immunodeficiency virus. Previously unvaccinated persons >59 months of age with one of these high risk conditions should be given at least one dose of any licensed Hib conjugate vaccine.

***Haemophilus influenzae* type b Vaccine**
Use in older children and adults

- **Generally not recommended for persons >59 months of age**
- **Consider for high risk persons: asplenia, immunodeficiency, HIV infection**
- **One pediatric dose of any conjugate vaccine**

Combination Vaccines

Several manufacturers have included Hib vaccine in combination with other vaccines. As of January 2000, there are 2 licensed vaccines that include whole cell DTP and Hib (Tetramune® and ActHIB/DTP™), one licensed DTaP-Hib combination vaccine (TriHIBit™), and a combination hepatitis B and Hib vaccine (COMVAX™).

Hib Combination Vaccines

- **Whole cell DTP - Hib**
  - **Tetramune**
  - **ActHIB/DTP**
- **DTaP - Hib (for 4th dose)**
  - **TriHIBit**
- **Hepatitis B - Hib**
  - **COMVAX**

Tetramune® and ActHIB/DTP™

ACIP recommends the use of acellular pertussis vaccine (DTaP) whenever possible. As of January 2000, no combination DTaP-Hib vaccine has been licensed for the primary series in infants. As a result, combination whole cell pertussis - Hib vaccines (Tetramune®, ActHIB/DTP™) is not recommended. The schedule for these combination vaccines is the same as for HbOC/PRP-T vaccines. Previously unvaccinated infants aged 2-6 months should receive three doses administered at least 2 months apart. An additional dose should be administered at 12-15 months of age, after at least a 6-month interval following the third dose.

TriHIBit

- **ActHIB reconstituted with Tripedia**
- **Use for 4th dose of series *only***
- **Should NOT use for first three doses of the series**

TriHIBit™

As of January 2000, only one combination of DTaP (acellular pertussis) and Hib (TriHIBit™)has been licensed. **This vaccine is currently licensed only for the fourth dose of the DTP-Hib series, after the child has been immunologically primed with Hib antigen**, either with single antigen Hib vaccine or with a whole cell DTP-Hib combination. Available data suggest that when a DTaP-Hib combination vaccine is given as the initial (priming) doses, response to the Hib component is reduced. This vaccine should not be used for any of the first three doses of the Hib series until it has been approved for this use by the Food and Drug Administration.

Infants Vaccinated with TriHIBit for the Primary Series

- **Primary series Hib doses given as TriHIBit *should be disregarded***
- ***Revaccinate* with single antigen Hib vaccine appropriate for age**

Infants who receive TriHIBit for any of the first three doses of the Hib series may not be protected against invasive Hib disease. Doses of TriHIBit given to an infant as the first, second, or third dose of the Hib series should be disregarded, and not counted as part of the Hib series. The child should be revaccinated with a single antigen conjugate Hib vaccine as appropriate for their age using the lapsed immunization guidelines (see above). The DTaP component does not need to be repeated.

COMVAX™

COMVAX™ is a combination hepatitis B-Hib vaccine, licensed in October 1996. The vaccine contains a standard dose of PRP-OMP (PedvaxHIB®), and 5 micrograms of Merck's hepatitis B vaccine. COMVAX™ is licensed for use when both antigens are indicated. However, Hib vaccine should not be given to infants <6 weeks of age because of the potential of immune tolerance to the Hib antigen.

COMVAX™ should not be used in infants <6 weeks of age (i.e., the birth dose of hepatitis B, or a dose at one month of age, if the infant is on a 0-1-6 schedule). COMVAX™ is not licensed for infants whose mothers are known to be hepatitis B surface antigen positive (i.e., acute or chronic infection with hepatitis B virus). However, the vaccine contains the same dose of Merck's hepatitis B vaccine recommended for these infants, so response to the hepatitis B component of COMVAX™ should be adequate.

COMVAX

- **Hepatitis B-Hib combination**
- **Use when both antigens indicated**
- **Cannot use <6 weeks of age**
- **Not licensed for use if mother HBsAg+**

Adverse Reactions Following Vaccination

Adverse events following Hib conjugate vaccines are uncommon. Swelling, redness, and/or pain have been reported in 5%-30% of recipients and usually resolve within 12-24 hours. Systemic reactions such as fever and irritability are infrequent. Available information on adverse events suggests that the risks for local and systemic events following Tetramune™ and ActHIB/DTP™ administration are similar to those following concurrent administration of its individual component vaccines, and are probably due to the pertussis component of the DTP vaccine.

***Haemophilus influenzae* type b Vaccine Adverse Reactions**

- **Swelling, redness, and/or pain in 5-30% of recipients**
- **Systemic reactions infrequent**
- **Serious adverse reactions rare**

All serious adverse events that occur after receipt of any vaccine should be reported to the Vaccine Adverse Events Reporting System (VAERS).

Contraindications and Precautions to Vaccination

Vaccination with Hib conjugate vaccine is contraindicated in persons known to have experienced anaphylaxis following a prior dose of that vaccine. Vaccination should be delayed in children with moderate or severe acute illnesses. Minor illnesses (*e.g.*, mild upper-respiratory infection) are not contraindications to vaccination.

***Haemophilus influenzae* type b Vaccine Contraindications and Precautions**

- **Severe allergic reactions to vaccine component or following previous dose**
- **Moderate to severe acute illness**

Contraindications and precautions for the use of Tetramune®, ActHIB/DTP™, TriHIBit™ and COMVAX™ are the same as those for its individual component vaccines (*i.e.*, DTP, DTaP, Hib, and hepatitis B).

Vaccine Storage and Handling

All Hib conjugate vaccines should be shipped in insulated containers to prevent freezing. Unreconstituted or liquid vaccine should be stored at refrigerator temperature (2°-8°C [35°-46°F]). Hib vaccine must not be frozen. Hib vaccines are stable for 30 days after reconstitution if the vaccine is stored at refrigerator temperature.

Opened multidose vials may be used until the expiration date printed on the package if they are not contaminated. ActHIB™ and TriHIBit™ should be used within 24 hours of reconstitution.

Surveillance and Reporting of Hib Disease

Invasive Hib disease is a reportable condition in most states. All health care workers should report any case of invasive Hib disease to local and state health departments.

Rifampin Prophylaxis

Several studies have shown that rifampin eradicated Hib carriage in >95% of contacts of primary Hib cases, including children in day-care facilities.

Contacts who develop symptoms suggestive of invasive Hib disease, such as fever or headache, should be evaluated promptly.

Rifampin chemoprophylaxis for **household contacts** is no longer indicated if all contacts aged <4 years are fully vaccinated against Hib disease. A child is considered fully immunized against Hib disease following (a) at least one dose of conjugate vaccine at 15 months of age; (b) two doses of conjugate vaccine at 12-14 months of age; or (c) two or more doses of conjugate vaccine at <12 months of age, followed by a booster dose at 12 months of age. In households with one or more infants <12 months of age (regardless of vaccination status) or with a child aged 1-3 years who is inadequately vaccinated, all household contacts should receive rifampin prophylaxis following a case of invasive Hib disease that occurs in any family member. The recommended dose is 20 mg/kg as a single daily dose (maximal daily dose 600 mg) for 4 days. Neonates (<1 month of age) should receive 10 mg/kg once daily for 4 days.

The use of rifampin in **day-care classrooms** is controversial. If a case of Hib disease has occurred, and any children less than 2 years of age have been exposed, all parents should be notified. Although data on risk are not optimal, all students (regardless of age) and staff in the classroom should receive rifampin prophylaxis according to the above regimen. However, rifampin prophylaxis is not necessary if all children <4 years of age are fully immunized.

Rifampin is contraindicated in pregnant women, as its effect on the fetus has not been established and it is teratogenic in laboratory animals.

Rifampin prophylaxis should be instituted as rapidly as possible. If more than 14 days have passed since the last contact with the index case, the benefit of rifampin prophylaxis is likely to be decreased.

The index case should be treated with the same rifampin regimen before discharge from the hospital, since antimicrobials used to treat invasive disease do not reliably eradicate carriage.

Children in day-care classrooms who are to receive chemoprophylaxis and who have received the Hib vaccine should also receive rifampin. However, if all children <4 years of age are fully immunized, chemoprophylaxis is not necessary.

Side effects may occur in up to 20% of recipients, and include nausea, vomiting, diarrhea, headache, and dizziness. Rifampin gets into body fluids exceptionally well and usually causes orange discoloration of urine. It may also cause discoloration of soft contact lenses and lens implants, or ineffectiveness of oral contraceptives.

Hib - Summary

- **<300 cases per year in infants**
- **Highest incidence in children <1 year of age**
- **Multiple vaccines and combinations**
- **Interchangeable**

Selected References

Bisgard KM, Kao A, Leake J, et al. *Haemophilus influenzae* invasive disease in the United States, 1994-1995: Near disappearance of a vaccine-preventable childhood disease. *Emerg Infect Dis 1998;4:229-37.*

CDC. *Haemophilus* b conjugate vaccines for prevention of *Haemophilus influenzae* type b disease among infants and children two months of age and older. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1991;40(RR-1):1-7.

CDC. Progress toward elimination of *Haemophilus influenzae* type b disease among infants and children — United States, 1987-1997. *MMWR* 1998;47:993-8.

CDC. *Haemophilus influenzae* invasive disease among children aged <5 years - California, 1990-1996. *MMWR* 1998;47:737-40.

Decker MD, Edwards KM, Bradley R, Palmer P. Comparative trial in infants of four conjugate *Haemophilus influenzae* type b vaccines. *J Pediatr* 1992;120:184-9.

Decker MD and Edwards KM. *Haemophilus influenzae* type b vaccines: history, choice and comparisons. *Pediatr Infect Dis J* 1998;17:S113-6.

Kostman JR, Sherry BL, Fligner CL, et al. Invasive *Haemophilus influenzae* infections in older children and adults in Seattle. *Clin Infect Dis* 1993;17(3):389-96.

Murphy TV, Pastor P, Medley F, Osterholm MT, Granoff DM. Decreased *Haemophilus* colonization in children vaccinated with *Haemophilus influenzae* type b conjugate vaccine. *J Pediatr* 1993;122:517-23.

Orenstein WA, Hadler S, Wharton M. Trends in vaccine-preventable diseases. *Semin Pediatr Infect Dis* 1997;8:23-33.

Peltola HH. *H. influenzae* in the post-vaccination era. *Lancet* 1993;341:864-5.

Peltola H, Aavitsland P, HansenKG, et al. Perspective: A five-country analysis of the impact of four different *Haemophilus influenzae* type b conjugates and vaccinations strategies in Scandinavia. *J Infect Dis* 1999;179:223-9.

Peter G, ed. *1997 Red Book: Report of the Committee on Infectious Diseases*. 24th ed. Elk Grove Village, IL: American Academy of Pediatrics, 1997.

Shapiro ED, Ward JI. The epidemiology and prevention of disease caused by *Haemophilus influenzae* type b. *Epidemiol Rev* 1991;13:113-42.